REMARKS

Claims 15 and 56 have been amended; claims 61-69 are newly added. Claims 36-55 and 57-60 remain pending. Claims 17-35 were previously canceled. Upon entry of this amendment, claims 15-16 and 36 to 69 will be pending.

Support for the amendments and new claims can be found throughout the specification and claims as originally filed, *e.g.*, at page 5, lines 10 to 23; page 6, lines 1 to 30; page 7, lines 4 to 29; page 8, lines 3 to 18; page 13, line 30, through page 14, line 1; page 17, line 11 to 28; page 18, lines 9 to 20; and Figures 2, 3, 5 and 6A. No new matter has been added.

The claim amendments made herein have been made solely to expedite prosecution of the instant application and should not be construed as an acquiescence to any of the Examiner's rejections.

Rejection of Claims 15, 16 and 36 to 60 under 35 U.S.C. §112, Second Paragraph

In paragraph 9 (pages 3 to 4) of the Office Action, the Office has maintained the rejection of claims 15, 16, and 36 to 60 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as their invention. More specifically, the Office alleges that "[t]he term 'relative' is a subjective term which is not defined. While those skilled in the art might be able to comprehend roughly what one might mean by using the term, ten different crystallographers will likely give ten different answers to what the metes and bounds of this limitation are." To support this conclusion, the Office asserts that:

> Because the world of protein crystallography deals in such a minute degree of measurements in angstroms (10×10^{-10} meters), an angstrom here or an angstrom there is an enormous variation and it is not clear from said limitation what the variance is or might be.

Applicants respectfully disagree with the Office's position that the term 'relative' as used herein is subjective and not well defined. The term 'relative' is used in the instant specification

and claims to qualify the term "structural coordinates" Applicants submit that the phrase "relative structural coordinates" is a term-of-art that describes the relationship between the atoms in a three dimensional structure. As defined in the specification and known in the art, this term refers to a constant relationship between the atoms in the coordinates, even though the entire three dimensional configuration can be shifted, *e.g.*, by rotation or inversion, integer addition or subtraction. Thus, although the actual number of the coordinates may vary, the relationship between the atoms remains constant. This is explained in the specification at page 15, lines 14 to 19, as follows:

> The structural coordinates of the present invention may be modified from the original sets provided in Figures 2, 3, 4, or 5 by mathematical manipulation, such as by inversion or integer additions or subtractions. As such, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of Figures 2, 3, 4, or 5. (Specification page 15, lines 14 to 19).

The Office also asserts that "Applicants own definition of "relative" structural coordinates on p. 15, line 7-19 of the specification states that the coordinates can come from NMR models, homology models, molecular replacement models all of which may be subject to various mathematical manipulations. Thus, the recitation of 'relative structural coordinates' appears to be non-limiting."

It is acknowledged that the structural coordinates in the three dimensional models used in the claimed methods can vary slightly. However, the degree of deviation from the three dimensional coordinates used in the claimed methods is provided by the "root mean square deviation," and not by the term "relative." The term "root mean square deviation" is defined in the instant specification at page 15, lines 22 to 24, as follows:

> "Root mean square deviation" is the square root of the arithmetic mean of the squares of the deviations from the mean, and is a way of expressing deviation or variation from the structural coordinates described herein. The present invention includes all embodiments comprising conservative substitutions of the noted amino acid residues resulting in the same structural coordinates within the stated root mean square deviation. *Id.*

Therefore, the pending claims require a limited deviation from the backbone atoms of Figures 2, 3, and 5 of no more than anywhere between 0.5 to 1.5 Å. Thus, the relative structural

coordinates encompassed by the three dimensional models in Figures 2, 3, and 5, as claimed, cannot be non-limiting, but include only those within the root mean square deviation parameters specified.

The Office has also newly rejected claims 15, 16, and 36 to 60 under 35 U.S.C. §112, second paragraph, stating that "there is a gap in the method steps because merely generically providing a crystal says nothing about subjecting said crystal to X-ray diffraction and solving the structure in order to obtain the structural coordinates." The Office also states that "[a]t the moment, the claims require nothing to be done to the crystal once it is provided so it is either a non-limitation in the claim which is surplus to requirement or said crystal needs to be positively acted upon and used in the method steps."

This aspect of this rejection has been met by amending independent claims 15 and 56 to include the step of "obtaining the relative structural coordinates of the crystallized P-selectin LE." Therefore, claims 15 and 56, as amended, link the step of providing a P-selectin LE crystal with the three-dimensional structures that are ultimately used in the claimed methods.

In view of the above remarks and amendments, Applicants request reconsideration and withdrawal of the rejection of claims 15, 16, and 36 to 60 under 35 U.S.C. §112, second paragraph.

Rejection of Claims 15, 16, and 36 to 60 for Lack of Enablement under 35 U.S.C, 112, First Paragraph

In paragraph 12 (pages 5 to 10) of the Office Action, the Office has rejected pending claims 15, 16, and 36 to 60 under 35 U.S.C, 112, first paragraph for alleged lack of enablement.

The Office states that "while being enabling for a method for identifying an agent that interacts with P-selectin LE by providing a crystal consisting of P-selectin LE selected from the group consisting of a) a P-selectin LE crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID NO:6" ... "b) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID NO:6 complexed with SLe^x" ... "c) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID NO: 8 complexed with PSGL-1 (SEQ ID NO:10)" ... "does not reasonably provide

enablement for the method which uses any P-selectin crystal." The Office additionally states that:

> Thus, the claim is unlimited in the number and variance of different P-selectin LE crystals that can be used in the claims because the protein within the crystal is not limited to any particular P-selectin protein. Thus the protein can be derived from a variety of species, wherein said proteins are also not limited to any particular specific protein sequence and thus would encompass any and every fragment, derivative or homolog of any of these P-selectin LE proteins. (Office Action, page 6)

This aspect of the rejection is now moot in view of the claim amendments to specify that the P-selectin LE sequence used in the claimed methods includes the amino acid sequence of SEQ ID NO:6, 8 or 9, or conservative substitutions thereof. It is noted that the human P-selectin LE sequences encompassed by the claimed methods may include one or more conservative substitutions of the amino acid sequence specified. The term "conservative substitutions" is defined in the specification as follows:

> [t]hose amino acid substitutions which are functionally equivalent to the substituted amino acid residue, either by way of having similar polarity, steric arrangement, or by belonging to the same class as the substituted residue (e.g., hydrophobic, acidic, or basic), and includes substitutions having an inconsequential effect on the three dimension structures of P-selectin LE, E-selectin LE, SLe^x, the PSGL-1 peptide, the P-selectin LE: SLe^x complex, the E-selectin LE:SLe^x complex, and the P-selectin LE: PSGL-1 peptide complex, with respect to the use of said structures for the identification and design of agents which interact with P-selectin LE, E-selectin LE, SLe^x, the PSGL-1 peptide, the P-selectin LE: SLe^x complex, the E-selectin LE:SLe^x complex, and the P-selectin LE: PSGL-1 peptide complex, as well as other proteins, peptides, molecules, or molecular complexes comprising an SLe^x or PSGL-1 binding site, for molecular replacement analyses and/or homology modeling. (Specification, page 16, lines 7 to 20).

Thus, the term "conservative substitutions" refers to those substitutions that have a requisite polarity, steric arrangement and/or belonging to the same class of substituted residue, such that the substituted residues remain within the root mean square deviation from the backbone atoms of P-selectin LE having the structural coordinates specified, *i.e.*, no more than anywhere between 0.5 to 1.5Å.

Moreover, newly added claims 61-65, which depend from independent claims 15 and 56, recite a particular group symmetry and unit parameter dimension of the crystals from which the structural coordinates are obtained. Thus, the claims, as amended or newly added herein, are no

longer directed to "any particular specific protein sequence and thus would encompass any and every fragment, derivative or homolog of any of these P-selectin LE proteins," but to methods for identifying agents that interact with P-selectin LE having the amino acid sequence specified, or conservative substitutions thereof, using three dimensional models generated using either the full structural coordinates according to Figures 2, 3 or 5, or the selected residues specified, ± a root mean square deviation from the backbone atoms of P-selectin LE of not more than 1.5Å.

Applicants submit that the present specification provides ample examples of P-selectin structural coordinates in complexed and free form to enable one of ordinary skill in the art to design and/or identify agents that interact with the P-selectin sequences recited in the claims. More specifically, the structural coordinates of human P-selectin in uncomplexed form and complexed with two different ligands, *i.e.*, SLe^x and PSGL-1, are disclosed in the specification in Figures 2, 3 or 5, respectively. In addition, the structural coordinates of E-selectin LE, another member of the selectin family, complexed with SLe^x was provided in Figure 4. The LE-domains of P- and E-selectin share 62% identity at the amino acid level. Therefore, the present applications describes the structural coordinates for P-selectin LE in three different forms, as well as the coordinates of a related selectin family member sharing 62% identity at the amino acid level complexed SLe^x.

In addition, the amino acid sequence and domain characterization of P-selectin LE were known in the art at the time the instant application was filed and are extensively described in the instant application. For example, a detailed characterization of the location of, and interactions between, residues and domains of P-selectin LE, and how these correlate with biological activity and binding to its receptor is provided, *e.g.*, starting on page 2, line 5 through page 5, line 8 of the instant application. The location of the lectin and EGF-like domains of P-selectin were also disclosed in the application. Selected residues important for receptor binding interaction are disclosed and claimed in the present application. Therefore, at the time the present application was filed, one of ordinary skill in the art would have known to make changes (e.g., conservative substitutions) to human P-selectin LE within the level of deviation required by the claims without undue experimentation. Techniques for generating mutant P-selectin LE proteins were well known in the art at the time the present application was filed and were performed routinely by molecular biologists. Similarly, high resolution crystallography and molecular modeling

techniques are extensively described in the instant application, and were known in the art at the time the application was filed. Software systems for generating three-dimensional models were also described in the specification, and were known in the art. Therefore, Applicants submit that following the teachings of the specification, one of ordinary skill in the art would have been able to generate P-selectin LE three dimensional models having the sequence specified or conserved variants thereof by practicing routine experimentation.

In another aspect of this rejection, the Office cites to several references as evidence of the high level of unpredictability in the state of the crystallography art. As discussed above, the claims, as presently pending, specify that the three dimensional model of the P-selectin structure used in the claimed methods includes the relative structural coordinates of the human P-selectin sequence specified, or selected residues located in the active site of human P-selectin, according to Figures 2, 3 or 5, ± a root mean square deviation from the backbone atoms of P-selectin of not more than 1.5Å. Accordingly, *de novo* crystallization of the P-selectin protein is not required to practice the claimed invention. It is clarified for the record that the pending claims encompass methods of designing an agent using three-dimensional models of P-selectin generated using crystals other than those described in the instant application, so long as the coordinates fall within the values shown in Figures 2, 3 or 5, ± a root mean square deviation from the backbone atoms of P-selectin of no more than 1.5Å.

As to the unpredictability of the crystallography art raised by the Examiner, it is acknowledged that establishing adequate protein crystallization conditions is a tedious and time-consuming process. However, this does not mandate a conclusion that the experimentation required for such process is necessarily undue as set forth by the enablement standard in *Wands* (858 F.2d 731) and re-articulated in the *Falkner* decision (448 F. 3d at 1365). Automated methods for speeding up "the tedious work of reproducibly setting up large numbers of crystallization experiments" were known in the art at the time the application was filed. *See e.g.*, Branden and Tooze, "Introduction to Protein Structure," Second edition, Garland Publishing Inc., New York (1999) at page 375. Methods of producing pure and homogeneous protein samples successful for crystallization can be readily obtained using recombinant techniques. *Id.* Even the crystallographic phase is characterized by Flower (2002) Drug Design, Cutting Edge Approaches, Royal Society of Chemistry, Cambridge, UK, as follows:

> However, even the recalcitrant discipline [crystallography phase] is yielding to the power of robotics and bioinformatics [citation omitted]. This allows many more trials to be performed and at much more accurately defined conditions than is the case for manual crystallizations. This has, in turn, led to the successful crystallization of many seemingly intractable proteins, such as several subunits from the lipocalin crustacyanin. Others have used sophisticated statistical techniques to speed the search for crystallization conditions but cutting down the number of conditions that needed to be tested. For example, robust multivariate statistics has been used to relate variations in experimental condition, within experimentally designed crystallization trials, to their results [citation omitted]. Although these mathematical models can not explain crystallization mechanisms, they do provide a powerful pragmatic tool allowing the setting up of crystallization trials in a more rational and more confident manner, particular when proteins are in limited supply. Flower reference at page 23.

In fact, the references cited by the Office in support of this rejection actually support the conclusions set out above by the Branden and Flower references. (*See* Cudney et al., pp. 1-7, Drenth et al., Chapter 1, p. 19, 4th paragraph, lines 1-2; and McPherson et al., p. 13). While Applicants acknowledge that each reference indeed discusses the tedious and intensive work in the field of protein crystallography, the Drenth reference provides that "[c]ommercially available robots make it possible to perform more experiments in the same time and to determine the optimum crystallization conditions more quickly" (Drenth, reference *supra*) and "[e]xperiments which in turn generated data that have led to the synthesis of factual generalization that we can use, together with common sense and scientific know how as powerful crystallization tools." ... "We now have access to a treasure chest of variables, screens, reagents, methods, and tools to crystallize biological macromolecules." (Cudney, reference *supra*).

Applicants submit that the present application satisfies the enablement requirement as set forth in the Federal Circuit's recent *Falkner* decision, discussed above. The court held that the claims directed to poxvirus vaccine vectors, for which no example was provided, were enabled by Inglis' application by stating that:

> The Board did not err in finding Inglis' claims to be enabled as a matter of law, in light of its articulated underlying factual findings. In support of its conclusion, it noted that "there is extensive disclosure of the selection of an essential gene, its deletion or inactivation and the production of a mutated virus with said deleted or inactivated gene, albeit for herpesvirus." Moreover, because the differences between the herpesviruses and poxviruses were well known, this would have

> aided the person of ordinary skill in the art in her application of the lessons of the herpesvirus example in the construction of poxvirus vaccines. The Board observed that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation." (448 F. 3d at 1365; emphasis added)

In view of the foregoing arguments, the claims as presently amended, the state of the art, the guidance provided by the specification, the present specification satisfies the enablement requirement. Accordingly, reconsideration and withdrawal of the rejection of the claims, as amended herein, is respectfully requested.

Rejection of Claims 15, 16, and 36 to 60 for Lack of Written Description under 35 U.S.C, 112, First Paragraph

In paragraph 14 (pages 10 to 14) of the Office Action, the Office has rejected pending claims 15, 16, and 36 to 60 under 35 U.S.C, 112, first paragraph for alleged failure to comply with the written description requirement. To support this conclusion, the Office states that:

> The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE. Thus the claims are intrinsically drawn to a large number of species of P-selectin crystals containing P-selectin proteins from any species and which are derivatives, homologues or fragments thereof and thus the claims possess a large genus of crystals. Also, as noted above, the crystal can have any ligand bound to the P-selectin LE. However, the specification only adequately describes three species in terms of both structure and function which belongs to this genus. (Office Action, page 10)

To expedite prosecution of the instant application, the claims, as amended or newly added herein, are directed to methods for identifying agents that interact with P-selectin LE having the amino acid sequence specified (*i.e.*, amino acid sequence of SEQ ID NO:6, 8 or 8, or conservative substitutions thereof), using three dimensional models generated using the full structural coordinates according to Figures 2, 3 or 5, or the selected residues specified, ± a root mean square deviation from the backbone atoms of P-selectin LE of not more than 1.5Å. Thus, the pending claims are no longer directed to "a large number of species of P-selectin crystals

containing P-selectin proteins from any species and which are derivatives, homologues or fragments thereof," and thus obviate this aspect of the rejection.

As acknowledged by the Office, the specification fully describes:

> [T]hree species of a P-selectin LE crystals [*sic*] that fall within the instant genera of crystals, those being: a) a P-selectin LE crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b=60.8 Å, c=91.4 Å and β=103.6°; b) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b=60.5 Å, c=91.4 Å and β=103.3°; and c) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) having space group 1222 with unit cell parameters of a=63.4 Å, b=96.8 Å and c=187.3Å. (Office Action, pages 11-12).

In fact, the structural coordinates of three species of human P-selectin in uncomplexed form and complexed to SLe^x and PSGL-1 were identified as set forth in Figures 2, 3 or 5, respectively, of the application. In addition, the structural coordinates of E-selectin LE, another member of the selectin family, complexed with SLe^x was provided in Figure 4. The LE-domains of P- and E-selectin share 62% identity at the amino acid level. Therefore, the present applications describes the structural coordinates for P-selectin LE in three different forms, as well as a related selectin family member sharing 62% identity at the amino acid level. Applicants respectfully submit that newly added claims 61-65, which depend from independent claims 15 and 56, recite the particular group symmetry and unit parameter dimensions quoted above of the crystals from which the structural coordinates are obtained. Thus, these claims, as presently amended, provide sufficient structural and functional characteristics in common with the species of the P-selectin LE three dimensional models used in the claimed methods to show that the Applicants were in possession of the claimed genus at the time of filing, and thus fully comply with the written description requirement.

With respect to the Office's position regarding the alleged high level of unpredictability in the state of the crystallography art, Applicants reiterate their position above. As discussed above, the claims, as presently pending, specify that the three dimensional model of the P-selectin structure used in the claimed methods includes the relative structural coordinates of the human P-selectin sequence specified, or selected residues located in the active site of human P-

selectin, according to Figures 2, 3 or 5, ± a root mean square deviation from the backbone atoms of P-selectin of not more than 1.5Å. Accordingly, *de novo* crystallization of the P-selectin protein is not required to practice the claimed invention. Following the structural coordinates set out in Figures 2, 3 or 5, the skilled artisan would have been able to design agents that interact with the P-selectin sequences specified in the claims.

Given the knowledge in the art and the teachings of the specification, a skilled practitioner at the filing date would have recognized that Applicants were in possession of, and had adequately described, the P-selectin LE genus recited in the pending claims to satisfy the standard set forth in the MPEP (*see, e.g.*, MPEP §2163(II)(A)(3)(ii)). Accordingly, Applicants submit that the claims, as presently pending, fully satisfy the written description requirement and reconsideration of this rejection is respectfully requested.

Enclosed is a $50.00 check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 16163-004001.

Respectfully submitted,

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